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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,052	DIRKS ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *44-47 and 52-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-43 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 26-43, and 48-51, in the reply filed on 4/27/2007 is acknowledged.

2. Claims 44-47 and 52-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/27/2007.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 31, 34, 39-40, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 31 recites the limitation "the restriction fragment" in claim 26. There is insufficient antecedent basis for this limitation in the claim.

b. Claim 34 is confusing because it cannot be determined what is encompassed by "a conserved splice site border sequence." It is unclear what the sequence entails and the specification does not provide further clarification.

c. Claims 39-40 recite the limitation "the consensus sequence" in claim 26. There is insufficient antecedent basis for this limitation in the claim.

d. Claim 48 is confusing because it is unclear how the claim further limits claim 43. The claim requires the step of "enriching the sample according to a method according to claim 43," and does not provide any further limitations to the method of claim 43. Furthermore, the use of "a method," renders the claim further confusing since it is not directly referring to *the* method of claim 43.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 26, 30-32, 34, and 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Caskey et al. (US 5,582,989).

Regarding claim 26, Caskey et al. teach a method for analyzing or amplifying a nucleic acid sequence, comprising analyzing or amplifying a nucleic acid with an S3P primer (i.e. col.3, lines 1-8; col.4, lines 49-52 wherein "the oligonucleotide primer is usually selected for its ability to anneal to intron sequences in the proximity of the 5' or 3' end of the exon or to anneal to a sequence at the intron-exon junction;" col.11, lines 6-8).

Regarding claims 30-31, Caskey teaches the nucleic acid sequence contains or is suspected to contain, an intron-exon junction and/or a splice site (see tables 2-10, descriptions of the tables, and col.10, lines 59-63).

Regarding claims 32, 34, and 36, Caskey teaches the S3P primer is in an intron-to-exon orientation or in an exon-to-intron orientation [claim 32], comprises a conserved splice site border sequence or at least part of a consensus sequence [claim 34], and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods [claim 36] (see col. 11, lines 6-8, where Exon 17 is from 227 to 402 and the second primer sequence used to amplify this sequence is from nucleotides 396 to 421 "intron-to-exon orientation").

Regarding claims 37-40, Caskey teaches the method of claim 26, wherein the S3P primer contains a total of between 8 and 20 nucleotides and between 4 and 10 nucleotides present in the S3P primer are complementary to the conserved region or consensus sequence of the splice site (see col. 4, lines 40-45, and col. 11, lines 6-8).

7. Claims 26, 30-32, 37, and 39-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Nicholson, Geoffrey Charles (US 7,105,480 B1).

Regarding claims 26, 30-32, 37, and 39-40, Nicolson teaches a method for analyzing or amplifying a nucleic acid sequence, comprising analyzing or amplifying a nucleic acid with an S3P primer (see Example 3, col.11, lines 45-65, and Table 4,

particularly, "all primer pairs spanned intron-exon splice sites allowing for detection for mRNA only" and primer of SEQ ID NO:7 is 20 nucleotides in length).

8. Claims 26, 30-32, 34, and 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomann et al. (WO 01/53529 A2).

Regarding claim 26, 30-32, Thomann et al. a method for analyzing or amplifying a nucleic acid sequence, comprising analyzing or amplifying a nucleic acid with an S3P primer [claim 26], wherein the nucleic acid sequence contains or is suspected to contain, an intron-exon junction and/or a splice site [claim 30] and the S3P primer is in an intron-to-exon orientation or in an exon-to-intron orientation [claim 32] (see pg.3, lines 24-29; pg.4, lines 5-15; pg.13, lines 13-25; pg.14, lines 23-25; pg. 15, lines 15-18; pg.16, Table IV, primers 6 and 8; pg.17, line 16; pg.26-27 Table VII, primers 947L (13) and 950U (14) and description of Table VIII).

Regarding claims 34, 36, and 39-40, Thomann teaches the method wherein the S3P primer comprises a conserved splice site border sequence or at least part of a consensus sequence, and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods (see pg.4, lines 5-15, pg.13, lines 13-25 and pg.10, lines 8-9).

Regarding claims 37-38, Thomann teaches the method wherein the S3P primer contains a total of between 8 and 20 nucleotides or wherein between 4 and 10

nucleotides present in the S3Pprimer primer are complementary to the conserved region or consensus sequence of the splice site (see pg.10, lines 1-2; Table IV, primers 6 and 8; pg.17, line 16; pg.26-27 Table VII, primers 947L (13) and 950U (14) and description of Table VIII).

9. Claims 26-32, 39-43, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardy et al. (US 5,973,133).

Hardy et al. teach a method for analyzing or amplifying a nucleic acid sequence, comprising analyzing or amplifying a nucleic acid with an S3P primer [claim 26, and 41-43], wherein said S3P primer is in combination with at least one AFLP primer [claim 27], and wherein the nucleic acid sequence comprises a restriction fragment to which one adapter sequence has been ligated [claim 28, and 41-43], or wherein the restriction fragment to which the adapter sequence has been ligated is part of a mixture of adapter-ligated restriction fragments [claim 29, and 41-43]. Hardy teaches the method wherein the nucleic acid sequence contains or is suspected to contain, an intron-exon junction and/or a splice site [claim 30] and the S3P primer is in an intron-to-exon orientation or in an exon-to-intron orientation [claim 32] (see Example 3, col.8, wherein PAC DNA is digested with blunt-cutting restriction enzymes, and then ligated to a specifically designed linker, generating a mixture of adapter-ligated restriction fragments, and the fragments are subsequently amplified using a linker-derived primer and an S182 exon-derived primer for exon/intron boundary sequencing. The primer

inherently is either in an intron-exon or exon-intron orientation. The products were recovered and analyzed via sequencing using a low-melting-point agarose).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 27-29, 33, 35, 41-43, and 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caskey et al. (US 5,582,989) as applied to claims 26, 30-34, and 36-40 above, and further in view of Vos et al., "AFLP, A new technique for DNA fingerprinting," Nuc.Acids.Res., 1995, Vol.23, No.21, pp.4407-4414, as cited on the IDS dated 1/3/06.

The teachings of the primary reference are discussed above. This reference does not discuss the method wherein the S3P primer is in combination with at least one AFLP primer [claim 27], and wherein the nucleic acid sequence comprises a restriction fragment to which one adapter sequence has been ligated [claim 28, and 41-43, 48], or wherein the restriction fragment to which the adapter sequence has been ligated is part of a mixture of adapter-ligated restriction fragments [claim 29, and 41-43, 48]. They do not teach the method wherein the AFLP primer contains at least one selective nucleotide at its 3' end [claim 33], or wherein the S3P primer further comprises a random sequence [claim 35].

Vos et al. teach a method of AFLP, comprising restriction digestion of genomic DNA, ligation of adaptors, amplification using adaptor-specific primers, and separation and analysis of the amplification reaction products via gel electrophoresis (see abstract; pg.4408, AFLP reactions; and pg.4409, Gel Analysis). Vos also teaches such primers comprising 0-3 selective nucleotides on the 3' end (see pg.4408, AFLP primers and adapters, and AFLP reactions, 3rd paragraph).

One of ordinary skill in the art would have been motivated to modify the method of Caskey et al. to further use at least one AFLP primer, ligate an adaptor to the ends of restriction digested DNA and amplify the adapter-ligated fragments with an SP3 primer, or add at least one selective nucleotide or a random sequence on the AFLP or SP3 primer, respectively, because Vos states that the AFLP technique is robust, reliable, permits the detection of restriction fragments in any background or complexity, bridges the gap between genetic and physical maps, and is a very effective tool to reveal

restriction fragment polymorphisms. Furthermore, Vos also notes that the addition of nucleotides on the primers causes a reduced number of bands and provides an effective way to select the desired number of fragments for amplification (pg.4410, 2nd col., 3rd paragraph, and pg.4411, 2nd col., 2nd paragraph). Therefore, the skilled artisan would have had a reasonable expectation of success in using at least one AFLP primer, ligating an adaptor to the ends of restriction digested DNA and amplifying the adaptor-ligated fragments with an SP3 primer, as well as adding additional nucleotides to the AFLP or SP3 primer in the method of Caskey et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed AFLP primer, adaptor-ligation PCR, and AFLP or SP3 primers with additional nucleotides/sequences therein.

13. Claims 27-29, 33, 35, 41-43, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicholson, Geoffrey Charles (US 7,105,480 B1) as applied to claims 26, 30-32, 37, and 39-40 above, and further in view of Vos et al., "AFLP, A new technique for DNA fingerprinting," Nuc.Acids.Res., 1995, Vol.23, No.21, pp.4407-4414, as cited on the IDS dated 1/3/06.

The teachings of the primary reference are discussed above. This reference does not discuss the method wherein the S3P primer is in combination with at least one AFLP primer [claim 27], and wherein the nucleic acid sequence comprises a restriction fragment to which one adapter sequence has been ligated [claim 28, and 41-43, 48], or wherein the restriction fragment to which the adapter sequence has been ligated is part of a mixture of adapter-ligated restriction fragments [claim 29, and 41-43, 48]. They do

not teach the method wherein the AFLP primer contains at least one selective nucleotide at its 3' end [claim 33], or wherein the S3P primer further comprises a random sequence [claim 35].

Vos et al. teach a method of AFLP, comprising restriction digestion of genomic DNA, ligation of adaptors, amplification using adaptor-specific primers, and separation and analysis of the amplification reaction products via gel electrophoresis (see abstract; pg.4408, AFLP reactions; and pg.4409, Gel Analysis). Vos also teaches such primers comprising 0-3 selective nucleotides on the 3' end (see pg.4408, AFLP primers and adapters, and AFLP reactions, 3rd paragraph).

One of ordinary skill in the art would have been motivated to modify the method of Nicholson, Geoffrey Charles to further use at least one AFLP primer, ligate an adaptor to the ends of restriction digested DNA and amplify the adapter-ligated fragments with an SP3 primer, or add at least one selective nucleotide or a random sequence on the AFLP or SP3 primer, respectively, because Vos states that the AFLP technique is robust, reliable, permits the detection of restriction fragments in any background or complexity, bridges the gap between genetic and physical maps, and is a very effective tool to reveal restriction fragment polymorphisms. Furthermore, Vos notes that the addition of nucleotides on the primers causes a reduced number of bands and provides an effective way to select the desired number of fragments for amplification (pg.4410, 2nd col., 3rd paragraph, and pg.4411, 2nd col., 2nd paragraph). Therefore, the skilled artisan would have had a reasonable expectation of success in using at least one AFLP primer, ligating an adaptor to the ends of restriction digested

DNA and amplifying the adaptor-ligated fragments with an SP3 primer, as well as adding additional nucleotides to the AFLP or SP3 primer in the method of Nicholson, Geoffrey Charles. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed AFLP primer, adaptor-ligation PCR, and AFLP or SP3 primers with additional nucleotides/sequences therein.

14. Claims 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicholson, Geoffrey Charles (US 7,105,480 B1), in view of Vos et al. (1995) as applied to claims 27-29, 33, 35, 41-43, and 48 above, and further in view of Thomann et al. (WO 01/53529 A2).

The teachings of the primary references are discussed above. These references do not discuss the method wherein the S3P primer comprises a conserved splice site border sequence or at least part of a consensus sequence, and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods.

The teachings of Thomann et al. are discussed above, specifically discussing the method wherein the S3P primer comprises a conserved splice site border sequence or at least part of a consensus sequence, and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods (see pg.4, lines 5-15, pg.13, lines 13-

25 and pg.10, lines 8-9).

One of ordinary skill in the art would have been motivated to modify the method of Nicholson, Geoffrey Charles and Vos et al. to target the SP3 primer to a conserved splice site border sequence, at least part of a consensus sequence, or a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods because Thomann et al. state that in order to study allelic variation and sequences pertinent to gene structure and phenotypic variation, it is necessary to analyze the entire chromosomal copy of a gene of interest which contain both exons and introns (see pg.2, lines 3-15), and demonstrate doing so by targeting primers to regions comprising consensus sequences, conserved splice site borders, and various splice sites. The skilled artisan would have had a reasonable expectation of success in targeting the SP3 primer to regions comprising consensus sequences, conserved splice site borders, and the various splice sites mentioned above in the method of Nicholson, Geoffrey Charles Nicholson, Geoffrey Charles and Vos et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed SP3 Primer targeted to the various splice sites and associated conserved border and consensus sequences therein.

15. Claims 34, 36, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicholson, Geoffrey Charles (US 7,105,480 B1) as applied to claims

26, 30-32, 37, and 39-40 above, and further in view of Thomann et al. (WO 01/53529 A2).

The teachings of the primary reference are discussed above. This reference does not discuss the method wherein the S3P primer comprises a conserved splice site border sequence or at least part of a consensus sequence, and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods.

The teachings of Thomann et al. are discussed above, specifically discussing the method wherein the S3P primer comprises a conserved splice site border sequence or at least part of a consensus sequence, and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods (see pg.4, lines 5-15, pg.13, lines 13-25 and pg.10, lines 8-9).

One of ordinary skill in the art would have been motivated to modify the method of Nicholson, Geoffrey Charles to target the SP3 primer to a conserved splice site border sequence, at least part of a consensus sequence, or a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods because Thomann et al. state that in order to study allelic variation and sequences pertinent to gene structure and

phenotypic variation, it is necessary to analyze the entire chromosomal copy of a gene of interest which contain both exons and introns (see pg.2, lines 3-15), and demonstrate doing so by targeting primers to regions comprising consensus sequences, conserved splice site borders, and various splice sites. The skilled artisan would have had a reasonable expectation of success in targeting the SP3 primer to regions comprising consensus sequences, conserved splice site borders, and the various splice sites mentioned above in the method of Nicholson, Geoffrey Charles. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed SP3 Primer targeted to the various splice sites and associated conserved border and consensus sequences therein.

16. Claims 27-29, 33, 35, 41-43, and 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomann et al. (WO 01/53529 A2) as applied to claims 26, 30-32, 34, and 36-40 above, and further in view of Vos et al., "AFLP, A new technique for DNA fingerprinting," Nuc.Acids.Res., 1995, Vol.23, No.21, pp.4407-4414, as cited on the IDS dated 1/3/06.

The teachings of the primary reference are discussed above. This reference does not discuss the method wherein the S3P primer is in combination with at least one AFLP primer [claim 27], and wherein the nucleic acid sequence comprises a restriction fragment to which one adapter sequence has been ligated [claim 28, and 41-43, 48], or wherein the restriction fragment to which the adapter sequence has been ligated is part of a mixture of adapter-ligated restriction fragments [claim 29, and 41-43, 48]. They do

not teach the method wherein the AFLP primer contains at least one selective nucleotide at its 3' end [claim 33], or wherein the S3P primer further comprises a random sequence [claim 35].

Vos et al. teach a method of AFLP, comprising restriction digestion of genomic DNA, ligation of adaptors, amplification using adaptor-specific primers, and separation and analysis of the amplification reaction products via gel electrophoresis (see abstract; pg.4408, AFLP reactions; and pg.4409, Gel Analysis). Vos also teaches such primers comprising 0-3 selective nucleotides on the 3' end (see pg.4408, AFLP primers and adapters, and AFLP reactions, 3rd paragraph).

One of ordinary skill in the art would have been motivated to modify the method of Thomann et al. to further use at least one AFLP primer, ligate an adaptor to the ends of restriction digested DNA and amplify the adapter-ligated fragments with an SP3 primer, or add at least one selective nucleotide or a random sequence on the AFLP or SP3 primer, respectively, because Vos states that the AFLP technique is robust, reliable, permits the detection of restriction fragments in any background or complexity, bridges the gap between genetic and physical maps, and is a very effective tool to reveal restriction fragment polymorphisms. Furthermore, Vos notes that the addition of nucleotides on the primers causes a reduced number of bands and provides an effective way to select the desired number of fragments for amplification (pg.4410, 2nd col., 3rd paragraph, and pg.4411, 2nd col., 2nd paragraph). Therefore, the skilled artisan would have had a reasonable expectation of success in using at least one AFLP primer, ligating an adaptor to the ends of restriction digested DNA and amplifying the adaptor-

ligated fragments with an SP3 primer, as well as adding additional nucleotides to the AFLP or SP3 primer in the method of Thomann et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed AFLP primer, adaptor-ligation PCR, and AFLP or SP3 primers with additional nucleotides/sequences therein.

17. Claims 33, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al. (US 5,973,133) as applied to claims 26-32, 39-43, and 48 above, and further in view of Vos et al., "AFLP, A new technique for DNA fingerprinting," Nuc.Acids.Res., 1995, Vol.23, No.21, pp.4407-4414, as cited on the IDS dated 1/3/06.

The teachings of the primary reference are discussed above. This reference does not discuss the method wherein the AFLP primer contains at least one selective nucleotide at its 3' end [claim 33], or wherein the S3P primer further comprises a random sequence [claim 35].

The teachings of Vos et al. are discussed above, specifically, teaching primers comprising 0-3 selective nucleotides on the 3' end (see pg.4408, AFLP primers and adapters, and AFLP reactions, 3rd paragraph).

One of ordinary skill in the art would have been motivated to modify the method of Hardy et al. to add at least one selective nucleotide or a random sequence on the AFLP or SP3 primer, respectively, because Vos states that the addition of nucleotides on the primers causes a reduced number of bands and provides an effective way to select the desired number of fragments for amplification (pg.4410, 2nd col., 3rd

paragraph, and pg.4411, 2nd col., 2nd paragraph). Therefore, the skilled artisan would have had a reasonable expectation of success in adding additional nucleotides to the AFLP or SP3 primer in the method of Hardy et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed AFLP or SP3 primers with additional nucleotides/sequences therein.

18. Claims 34, 36, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al. (US 5,973,133) as applied to claims 26-32, 39-43, and 48 above, and further in view of Thomann et al. (WO 01/53529 A2).

The teachings of the primary reference are discussed above. This reference does not discuss the method wherein the S3P primer comprises a conserved splice site border sequence or at least part of a consensus sequence, and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods. They also do not specifically discuss the method wherein the S3P primer contains a total of between 8 and 20 nucleotides or wherein between 4 and 10 nucleotides present in the S3Pprimer primer are complementary to the conserved region or consensus sequence of the splice site

The teachings of Thomann et al. are discussed above, specifically discussing the method wherein the S3P primer comprises a conserved splice site border sequence or

at least part of a consensus sequence, and is specific for a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods (see pg.4, lines 5-15, pg.13, lines 13-25 and pg.10, lines 8-9). Thomann also discusses the S3P primer containing a total of between 8 and 20 nucleotides and the method wherein between 4 and 10 nucleotides present in the S3Pprimer primer are complementary to the conserved region or consensus sequence of the splice site (see pg.10, lines 1-2; Table IV, primers 6 and 8; pg.17, line 16; pg.26-27 Table VII, primers 947L (13) and 950U (14) and description of Table VIII).

One of ordinary skill in the art would have been motivated to modify the method of Hardy et al. to target the SP3 primer to a conserved splice site border sequence, at least part of a consensus sequence, or a splice site selected from the group consisting of GU-AG introns, AU-AC introns, Group I introns, Group II introns, Group III introns, Twintrons, Pre-tRNA introns, and splice sites that are identified using computer based splice site identification methods, wherein the primer contains a total of between 8 to 20 nucleotides and between 4 and 10 nucleotides are complementary to the conserved region or consensus sequence of the splice site because Thomann et al. state that in order to study allelic variation and sequences pertinent to gene structure and phenotypic variation, it is necessary to analyze the entire chromosomal copy of a gene of interest which contain both exons and introns (see pg.2, lines 3-15), and demonstrate doing so by targeting primers to regions comprising consensus sequences, conserved

splice site borders, and various splice sites. Furthermore, they demonstrate the benefits of using primers which are between 8 to 20 nucleotides in length and have between 4 to 10 nucleotides which are complementary to the conserved region or consensus sequence of the splice site. Therefore, the skilled artisan would have had a reasonable expectation of success in targeting the SP3 primer, comprising such sequences at such lengths, to regions comprising consensus sequences, conserved splice site borders, and the various splice sites mentioned above in the method of Hardy et al.. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed SP3 Primer targeted to the various splice sites and associated conserved border and consensus sequences therein.

Summary

19. No claims are free of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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